APPENDIX

APPENDIX

Section 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052, as originally enacted and in force until October 10, 1962, provided in pertinent part:

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application

(1) full reports of investigations which have been made to show whether or not such drug is safe for use;

(2) a full list of the articles used as components of such drug;

(3) a full statement of the composition of such drug;

(4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and

(6) specimens of the labeling proposed to be used for such drug.

(c) An application provided for in subsection (b) shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date

of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application.

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that

(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;

(3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or

(4) upon the basis of the information submitted to him as part of the application or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

(e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds

(1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or

(2) that the application contains any untrue statement of a material fact. The order shall state the findings upon which it is based.

(g) Orders of the Secretary issued under this section shall be served

(1) in person by any officer or employee of the department designated by the Secretary or

(2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing to permit the application to become effective, or suspending the effectiveness of the application. Such appeal shall be taken by filing in the district court of the United States within any district wherein such applicant resides or has his principal place of business, or in the District Court of the United States for the District of Columbia, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. • • •

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Vol. 25, No. 5 February 4, 1963

F-D-C REPORTS
TRADEMARKS REG. U. S. PAT. OFFICE
1153 NATL. PRESS BLDG.
WASHINGTON 4, D. C.
Founded 1939 --- $150.00 a year

Drugs and Cosmetics
"The Pink Sheet"

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"GRANDFATHER CLAUSE" IN 1962 DRUG LAW COVERS: ALL DRUG PRODUCTS MARKETED ON OCT. 9 THAT WERE NOT SUBJECT, AT THAT TIME, TO AN ACTIVE NDA: FDA RULES

The "Grandfather Clause" in the 1962 drug law applies to every drug product marketed in the U.S. on Oct. 9, 1962 that was not covered at the time by an "active" New Drug Application (NDA).

Two groups of drug products are "grandfathered": (1) Those which never had an NDA; and (2) Those which were cleared through the NDA procedure but were subsequently transferred from "new drug" status by a letter from FDA.

This ruling, stated definitely and precisely by Deputy FDA Com. Harvey, clarified one of the most important and controversial questions that confronted both industry and govt. as a result of an apparent conflict between the language of the 1962 drug law and its legislative history.

Harvey stated the Food & Drug Administration's (FDA) interpretation in one sentence -- almost paranthetically -- in his recent speech before the Drug & Allied Product Guild (see quotation in box below). Expanding on the key half-sentence in his speech, he told "The Pink Sheet" that FDA believes the "Grandfather Clause" applies to every marketed drug product, not covered by an NDA, at a particular time -- Oct. 9, 1962.

**"GRANDFATHER CLAUSE"
1962 Drug Law
DEPUTY FDA COM. HARVEY:**

In the future, mfrs. of "new drugs" will therefore need to demonstrate their effectiveness....

There is a 2-year transitional period for drugs now having an effective new drug application before this requirement becomes effective, and drugs not now requiring a new drug application because of safety will not become new drugs under the effectiveness concept if claims and representations remain as they were at the time of the statute's enactment. This is the so-called "Grandfather Clause."

Language in the legislative history might have formed the basis for an FDA view that the "Grandfather Clause" covered only those drug products -- on the market Oct. 9 -- which had never been cleared through the NDA procedure.

The second Senate Judiciary Cmte. report on the bill said that: "Drugs which are commercially used at the time of enactment and which were never subject to the 'new drug' procedure before, shall not be considered 'new drugs' by reason of the new 'effectiveness' requirements added.... by the bill."

House Interstate Cmte.'s report also had a comparable statement. Had this legislative history been translated into the regulatory system, every drug product which had been NDA-ed since 1938 could have been placed under the NDA procedure again for the purpose of requiring substantial evidence to prove

its effectiveness. To remain under the protection of the "Grandfather Clause," a drug product must be sold only for the conditions prescribed, recommended or suggested in the labeling on Oct. 9.

A strong body of opinion at the FDA staff level favored the legislative history interpretation of the "Grandfather Clause." They wanted the effectiveness provision of the "new drug" section to cover as many products as possible. In short, they wanted the clause to cover the fewest number of products.

When the issue finally arrived at FDA's topside, practical considerations as well as legal interpretation pointed to the ruling that was adopted. FDA didn't want to discriminate between pioneer products that had been cleared through the NDA procedure and their follow-up products that had been marketed after the time when the pioneers were shifted from "new drug" to "old drug" status.

Some of the early cortical steroids, for example, were marketed after NDA clearance, but later were declared to be "old drugs" and many different brands were sold without going through the NDA procedure.

Another practical guide emerges from this line of FDA thinking. If a mfr. wants to market a new product today that is identical with a grandfathered product which was on the market Oct. 9, he probably will not have to process the new competitive product through the NDA procedure.

But he will have to check in with FDA to make certain that his new product is actually protected by the "Grandfather Clause." The checking in procedure could involve almost as much information as FDA required for clearance of "new drugs" under the NDA procedure a few years ago.

FDA Won't Ignore Effectiveness During Two-Year Grace Period For NDA-ed Products

Drug products marketed on last Oct. 9 and still subject to NDA coverage cannot be challenged directly under the effectiveness standard until Oct. 10, 1964. The law provided a two year grace period, but in the day-to-day operation of the NDA procedure, this may not mean very much.

The new law provides that FDA can move for the withdrawal of an NDA whenever it gets new evidence questioning the safety or effectiveness of a product. In strict legal terms, the withdrawal procedure shifts a burden of proof to the govt.

But FDA has seldom had to resort to formal legal procedures in administering the NDA system. In the past, operating mechanisms have been worked out to achieve a regulatory approach, and industry has at least acquiesced.

Whenever an NDA supplement raises an issue close to effectiveness, or even directs attention to a question of effectiveness, FDA can be expected to bring the matter up with the mfr. without waiting until Oct. 10, 1964.

FDA-ers feel they can get into trouble either way: If they hew strictly to the two-year grace period, they could be criticized, even by mfrs., for keeping mum on effectiveness questions when passing NDA supplements on corrolary matters. On the other hand they know they also can get in trouble by pressing effectiveness too hard or too far on existing products before Oct. 10, 1964. In an exchange of correspondence with PMA General Counsel John Worley, Deputy FDA Com. Harvey had promised there would be no "delay in handling acceptable supplements" to NDAs.

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F-D-C REPORTS
Vol. 25, No. 7 February 18, 1963

FDA'S FEB. 15 CONFERENCE ON NEW LAW SHOWS DISAGREEMENT BETWEEN DEPUTY COM. HARVEY & GENERAL COUNSEL GOODRICH ON COVERAGE OF THE "GRANDFATHER CLAUSE"

A disagreement among FDA topsiders over the meaning of the important "Grandfather Clause" in the 1962 drug law, which became apparent during the Q-&-A at the Feb. 15 "open conference," spotlighted the fluid state of govt. thinking in many areas of the new regulatory system, now being worked out.

Deputy FDA Com. Harvey, in a speech delivered Jan. 24, flatly declared that any drug product which did not have an "active" New Drug Application (NDA), as of Oct. 9, 1962, was protected by the "Grandfather Clause" from a requirement that the mfr. produce substantial data in support of its effectiveness -- providing no change is made in the product or its claims.

"GRANDFATHER CLAUSE"
1962 Drug Law
FDA COUNSEL GOODRICH

By a "grandfather clause," it means that the status of the drug on the date of the enactment is not changed by the enactment. The basic grandfather clause is that none of these requirements apply to a new drug which is generally recognized as both safe and effective.

For old drugs which are not generally recognized as safe, if they were on the market with never any clearance through the new drug procedures, they are permanently protected to use unsubstantiated claims, provided these claims are not changed.

The third phase of it is for a drug which was once cleared through the new drug procedures on an issue of safety alone, this is protected for two years in order to allow the sponsor to accumulate a scientific basis for making his claims.

This view was confirmed in an interview with Harvey, and was reported in the Feb. 4 issue of "The Pink Sheet." The same interpretation was repeated by Earl L. Meyers, New Drug chief chemist, in a comprehensive speech on the new law, delivered Feb. 8.

(EDITORS' NOTE: The quotation from Harvey's Jan. 24 speech, appearing in the box on the next page, is reprinted from the Feb. 4 issue of "The Pink Sheet.")

W. W. Goodrich, FDA's general counsel, however, took another view on the "Grandfather Clause" when he answered a series of questions at the Feb. 15 "open conference."

In the presence of an SRO audience -- about 750 -- he disagreed with Harvey's earlier interpretation, and gave the opinion that the "Grandfather Clause in effect, gives full protection only to drug products that have never been cleared through the NDA procedure.

(EDITORS' NOTE: See box at the left for full text of one of Goodrich's several answers to the same question. All of them were consistent.)

After the "open conference," Harvey acknowledged to "The Pink Sheet" that there was a difference in views on the question between Goodrich and himself. The deputy commissioner said this indicates FDA's final view is not firmed up yet and will have to be thrashed out.

S-2

[Continuation of story omitted]

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394, 72-414, 72-528, 72-555 and 72-666

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs, *Petitioners and Respondents,*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Respondent and Cross-Petitioner.*

CIBA CORPORATION, *Petitioner,*

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs, *Petitioners,*

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

USV PHARMACEUTICAL CORPORATION, *Petitioner,*

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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INDEX

	Page
Motion for Leave to File Brief Amici Curiae	2
Brief Amici Curiae	7
Statement of Interest of Amici Curiae	8
Introduction	8
I. THE 1962 AMENDMENTS, WHICH ARE ONLY NOW BEGINNING TO BE ENFORCED, ARE AN IMPORTANT PROTECTION FOR CONSUMERS	11
II. THESE CASES PRESENT THREE DISTINCT BUT INTERRELATED ISSUES THAT ARE CRUCIAL TO MEANINGFUL ENFORCEMENT OF THE 1962 AMENDMENTS	17
III. A DECISION ADVERSE TO FDA ON ANY OF THESE ISSUES WILL, AS A PRACTICAL MATTER, PREVENT EFFECTIVE ENFORCEMENT OF THE ACT AND THWART THE CONGRESSIONAL PURPOSE TO REMOVE INEFFECTIVE DRUGS FROM THE MARKET	21
A. The Efficacy Requirement Added By The 1962 Amendments Is An Important Protection For Consumers	22
B. A Decision Adverse To FDA Will Frustrate Enforcement Of The 1962 Amendments As To Pre-1962 Drugs	22
C. An Adverse Decision Will Also Threaten Enforcement Of The 1962 Amendments With Respect to Post-1962 Drugs	28

INDEX—Continued

Page

D. The Fourth Circuit's Decisions, If Sustained, Will Undermine FDA's Aggressive New Effort To Enforce The Act, For The First Time, Against Over-The-Counter Drugs 30

E. Misbranding Actions Are No Substitute For The Efficacy Requirements Adopted In The 1962 Amendments 32

IV. FDA'S ENFORCEMENT PROGRAM IS TOTALLY CONSISTENT WITH THE STATUTORY LANGUAGE AND HISTORY 33

A. Congress Intended The 1962 Efficacy Requirement To Apply To Both Previously NDA'd Drugs and Their Copies 33

B. FDA Has Jurisdiction To Decide, In The First Instance, What Is A "New Drug" and When A Drug Is A Copy 36

C. FDA Need Not Accord A Full Evidentiary Hearing When The Manufacturer Produces No Scientific Studies That Meet The Statutory And Regulatory Criteria 38

Conclusion 40

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394 and 72-414

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Petitioners and Respondents,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,

Respondent and Cross-Petitioner.

No. 72-528

CIBA CORPORATION,
a corporation of the State of Delaware,

Petitioner,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

---

No. 72-555

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

No. 72-666

USV PHARMACEUTICAL CORPORATION,
Petitioner,
v.
CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

---

MOTION FOR LEAVE TO FILE BRIEF AMICI CURIAE IN SUPPORT OF THE UNITED STATES ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION, THE NATIONAL COUNCIL OF SENIOR CITIZENS, AND CONSUMERS UNION OF UNITED STATES, INC.

The American Public Health Association, National Council of Senior Citizens, and Consumers Union of United States, Inc., hereby respectfully move for leave to file the attached brief *amici curiae* in support of the United States in these cases. The consent of the United States has been obtained and has been filed with the Clerk of this Court. The consent of all the pharmaceutical manufacturers was not obtained.

The American Public Health Association and National Council of Senior Citizens were previously granted permission to file a brief *amici curiae* in support of the Government's petition for certiorari in one of these cases, *Richardson* v. *Hynson, Westcott and Dunning*, No. 72-394.

The interest of these two *amici* in these cases arises in part from their recent successful court action in United States District Court for the District of Columbia against

the Food and Drug Administration, *American Public Health Association* v. *Veneman*, C.A. No. 1847-70 (August 23, 1972). The 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 require the Food and Drug Administration (FDA) to withdraw from the market drugs first introduced between 1938 and 1962 for which there is no "substantial evidence" of effectiveness. FDA did not begin to act to implement this mandate for nearly a decade, and thousands of ineffective drugs are still being sold. The District Court in *Veneman* found that FDA had in effect "stayed" implementation of the Act and directed FDA to proceed "expeditiously" to withdraw ineffective drugs from the market, pursuant to a court-established timetable.

In the attached brief, *amici* demonstrate that the decisions of the Court of Appeals for the Fourth Circuit in three of the four cases now before this Court would, if sustained, as a practical matter block compliance by FDA with the order of the District Court in *American Public Health Association* v. *Veneman*. *Amici* seek to file a brief supporting the United States in order to protect the interest of the public in enforcement of this extremely important statute, as interpreted in the *Veneman* case.

In the brief, *amici* do not seek to reiterate the legal arguments of the parties in each case, but to identify several major issues crucial to enforcement of the 1938 Act that are raised by the cases taken together, and to show some of the practical ramifications of these issues.

All three *amici* have had a long-standing concern for protecting the public from the abuses of ineffective drugs. The American Public Health Association is a national professional organization whose membership of over 26,000 consists primarily of professional public health workers, including doctors, nurses, and hospital administrators. The Association, which was 100 years old last year, was

organized to provide public health professionals with a vehicle for influencing national and local public health policy. It publishes a monthly magazine, the *American Journal of Public Health*, consisting of papers from its membership, and a monthly newspaper, *The Nation's Health*. Concern with this country's drug problem, including drug ineffectiveness, dominated a major part of the 1972 annual meeting of the Association. As a result, several resolutions were adopted supporting broader regulation of the drug industry and increased appropriations to FDA and other federal agencies charged with the responsibility of safeguarding the public's health.

The National Council of Senior Citizens, formed in 1961, is a non-profit association of over 3,000 senior citizen groups from different states with a combined membership of over 3,000,000 elderly people. The purpose of the organization is to provide education and to act as a national clearinghouse on matters of interest to senior citizens. The interest of the elderly in drug effectiveness is a critical one. Of people 65 and older, over 85 percent are suffering from one or more chronic conditions and, as a result, elderly people use three times the amount of drugs as the average American citizen. This need for drugs—coupled with the fact that one out of four of the 22 million persons under the poverty line of $1,900 a year is over the age of 65—makes the problem of costly and ineffective drugs an extremely important matter for senior citizens. In view of the importance of drugs to the elderly, the Council has actively participated in drafting legislation to extend Medicare coverage to out-of-hospital drugs, and joined with two other organizations in 1966 to form a drug cooperative in an effort to reduce the rising cost of drugs.

Consumers Union of United States, Inc., with approximately 350,000 members, is the largest consumer organization in the United States. It was organized in 1936

as a non-profit corporation under the laws of New York to provide information and counsel to consumers concerning goods and services. Consumers Union engages in extensive testing of products and publishes test results and general consumer information in its monthly magazine, *Consumer Reports*, which has a paid circulation of approximately 2.2 million readers. On behalf of its members, Consumers Union takes public positions on many significant issues of importance to consumers and advances those positions before administrative agencies and the courts.

In numerous articles over the years, *Consumer Reports* has informed its members about activities of FDA with respect to the safety and efficacy of drugs. Consumers Union has published a book on the safety and efficacy of over-the-counter drugs, entitled *The Medicine Show*. In December, 1972, Consumers Union brought an action in the United States District Court for the District of Columbia to compel FDA to implement its earlier final order withdrawing marketing approval for a drug that failed to meet the efficacy requirement of the 1962 Amendments. *Consumers Union* v. *Richardson, et al.*, C.A. No. 2498-72.

The filing of the brief *amici curiae* is timely. Petitioners' briefs in these cases were required to be filed by March 1, 1973, and all respondents' briefs (including those of the United States in *Ciba*, *USV*, and *Hynson*, No. 72-414) thirty days later. By permission of the Clerk of the Court, since the *amici* brief is a consolidated brief covering all the cases, *amici* were permitted to file their brief pursuant to the time schedule established for the United States as respondent. In fact, printed briefs in *USV* and *Bentex* and the brief of the United States as Petitioner in *Hynson*, No. 72-394, were not filed until the week following March 1, 1973. Since Petitioner USV filed a typed copy of its brief on March 1, *amici* were requested by the Clerk to file ten typewritten copies of

their brief on or by March 31 and to file the requisite number of printed copies immediately thereafter.

CONCLUSION

For the foregoing reasons, we respectfully submit that the Motion to File Brief *Amici Curiae* in Support of the United States should be granted.

Respectfully submitted,

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BRUCE J. TERRIS

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

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USV PHARMACEUTICAL CORPORATION,
Petitioner,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs.

BRIEF AS AMICI CURIAE IN SUPPORT OF THE UNITED STATES ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION, THE NATIONAL COUNCIL OF SENIOR CITIZENS, AND CONSUMERS UNION OF UNITED STATES, INC.

STATEMENT OF INTEREST OF AMICI CURIAE

The interest of *amici curiae* is fully described in the Motion for Leave to File Brief Amici Curiae above.

INTRODUCTION

In the Food, Drug and Cosmetic Act of 1938, as amended in 1962, Congress provided that all drugs sold to the American public shall be both safe and effective for their intended uses. But, for reasons we develop in this brief, the Congressional mandate embodied in the Act has never been carried out with respect to *ineffective* drugs whose withdrawal from the market was required by the 1962 Amendments.

It was not until 1969 and 1970 that the Food and Drug Administration [hereinafter FDA] began to adopt procedures and initiate actions essential to vigorous en-

forcement of the Act and protection of the American consumer. The overriding issue before the Court in these four cases is whether FDA's belated but salutary efforts to implement this Act will be stymied and the clear Congressional intent to remove ineffective drugs from the market permanently thwarted.

In this brief, *amici* do not reiterate all the legal arguments supporting FDA's enforcement program, which are exhaustively reviewed in the briefs for the United States. FDA's program is totally consistent with the statutory scheme and is designed to afford maximum fairness to drug producers and the most effective protection to consumers. Most courts that have recently considered aspects of FDA's regulatory approach have sustained and commended it,[1] and one District Court, in an action brought by two of *amici curiae*, has even held that it is not proceeding fast enough.[2]

Rather, *amici* seek to (1) identify from the mass of material surrounding these cases the three distinct legal issues that are posed, and (2) demonstrate why, as a practical matter, acceptance by this Court of the restricted and distorted view of the Act pressed by the drug manufacturers would bring FDA's encouraging new efforts to implement the Act to a halt.

Accordingly, this brief treats the four cases in a coordinated fashion and discusses at some length matters not fully explored in the briefs of the parties, including

[1] See Upjohn Co. v. Finch, 422 F.2d 944 (CA 6, 1970); Pfizer, Inc. v. Richardson, 434 F.2d 536 (CA 2, 1970); Ciba-Geigy Corp. v. Richardson, 446 F.2d 466 (CA 2, 1971); American Cyanamid Co. v. Richardson, 456 F.2d 509 (CA 1, order of one judge denying stay); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del. 1970).

[2] American Public Health Association v. Veneman, CA No. 1847-70 (D.D.C. Aug. 23 and Oct. 11, 1972), discussed at page 16, *infra*.

the importance of the effectiveness requirement, the dimensions of the enforcement problem with respect to both prescription and over-the-counter drugs, and the practical ramifications of a decision adverse to FDA.

The drug manufacturing industry originally opposed adoption of the provisions enacted in 1962, which require withdrawal of ineffective drugs from the market, on the ground that such measures were unnecessary, and it has fought their effective enforcement since 1962.[3] Its briefs in these cases are conspicuously devoid of any reference to the important goals Congress sought to achieve by this legislation. The reason for this is that the legal positions the industry espouses are fundamentally inconsistent with the Congressional purpose. These cases represent the final chapter in the drug manufacturers' efforts to undo in the courts what they were unable to prevent Congress from doing in 1962.

This Court need not and should not read the Act to disable the expert administrative agency charged with attaining its important public health and consumer goals from doing so. Rather, the Court should construe the Act in harmony with the purposes for which it was enacted.

This brief will:

I. Describe, by summarizing the operation of the Act and its enforcement by FDA, how meaningful enforcement of the 1962 Amendments has been delayed for over a decade;

---

[3] See Jurow, The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments, 19 Food Drug Cosm. L.J. 110 (1964); Mintz, FDA and Panalba, A Conflict of Commercial, Therapeutic Goals?, 165 Science 875 (1969). Commissioner Ley, in 1969, characterized the industry's resistance to the 1962 Amendments as "intense and prolonged." Hearings on Drug Efficacy Before a Subcomm. of the House Comm. on Government Operations, 91st Cong., 1st Sess., pt. II, at 238.

II. Summarize, for the Court's convenience, the three distinct but interrelated legal issues crucial to continued enforcement of the Act that are presented by the four cases before it;

III. Demonstrate that the position urged by the drug manufacturers on each of these three issues would, as a practical matter, block FDA's enforcement of the Act and indefinitely thwart the Congressional mandate that ineffective drugs be removed from the market; and

IV. Show briefly, with respect to each issue, that FDA's regulatory program is fully consistent with the statutory language and history, as well as the purposes of the Act.

I. THE 1962 AMENDMENTS, WHICH ARE ONLY NOW BEGINNING TO BE ENFORCED, ARE AN IMPORTANT PROTECTION FOR CONSUMERS.

In 1938 Congress, in the wake of a major drug tragedy, first provided for pre-marketing administrative clearance of pharmaceuticals sold in interstate commerce, to assure the public that such drugs would be safe for their recommended uses. Federal Food, Drug and Cosmetic Act, 52 Stat. 1040. The pre-marketing clearance scheme did not apply to every drug brought on the market after 1938, but only to those drugs not already "generally recognized" by qualified experts as "safe." Drugs not so recognized were defined by the Act as "new drugs". The clearance scheme established by the 1938 Act was in large part self-policing. The manufacturer itself was required to determine whether a drug was a "new drug" within the meaning of the Act, and if so, to submit a "new drug application" [hereinafter NDA] to the FDA setting out scientific evidence of the drug's safety. The NDA automatically became effective, and the manufacturer could then market its drug unless, within a specified period of

time, FDA (after notice and opportunity for hearing) decided that the evidence did not establish the drug's safety, and disapproved the application.[4] (NDA's could also be later withdrawn by FDA on the same grounds.) The self-policing aspect of the scheme was, however, supplemented by powerful incentives to manufacturers to seek clearance in doubtful cases. The Act gave FDA power to seek an injunction in District Court against distribution of non-NDA'd "new drugs" and to seize such drugs in condemnation and libel proceedings. Marketing of a "new drug" without an effective NDA could also be made the basis for a criminal prosecution.

The large volume of NDA's received by FDA relative to its comparatively small staff and the paramount need to protect the public from potential hazards of brand new drug ingredients gave rise to an administrative anomaly that has become central to resolution of these four cases: the "me-too" problem. When one manufacturer obtained an effective NDA for a "new drug" containing some new compound or active ingredient not theretofore generally recognized as safe, other manufacturers often rushed to produce and market the identical or a substantially similar drug containing the same ingredient, but under a different trade name or under the generic name. On occasion, a manufacturer would even market copies of its own drug. Sometimes manufacturers filed independent NDA's on these copies or so-called "me-too" drugs. More often they did not, apparently taking the position that because the pioneer drug was already being marketed under an effective NDA, its basic ingredient had been demonstrated to FDA to be "safe", and the copy therefore did not require an NDA. Some manufacturers re-

[4] The 1938 Act provided that orders denying or suspending an NDA were reviewable on the administrative record in the District Courts. The 1962 Amendments provided for direct review of such orders in the Court of Appeals. § 505(h), 21 U.S.C. § 355(h).

quested advisory opinions from FDA on these "me-too" drugs and, in some cases, received opinions that no NDA was required to be filed.

The dimensions of this problem were considerable. The 1940's and 1950's were the heyday of prescription drug development, and it is estimated that for every NDA'd pioneer new drug, five to thirteen "me-too" copies were also brought on the market.[5]

Whether the manufacturers' individual exemption claims for "me-too" drugs were valid in most cases, and indeed whether FDA's overall treatment of "me-too" drugs was consistent with the statutory requirement of pre-marketing clearance for *all* "new drugs" were questions never considered or decided by any court. As a practical matter, FDA was forced by its limited resources and the overriding need to protect the public from dangerous new drug ingredients to adopt this short-cut approach to "me-too's", and the manufacturers had no cause to complain.

In 1962, Congress made three major changes in the 1938 Act it thought necessary to afford adequate protection to the public. Harris-Kefauver Amendments of 1962, 76 Stat. 781. First, the 1962 Amendments provided that no "new drug" could go on the market without *affirmative* approval by the FDA of the filed NDA. Second, they amended the definition of "new drug" to include any drug not already recognized by qualified experts as "safe *and effective*". Thus, as to drugs coming on the market for the first time after 1962, manufacturers would be required to file NDA's on all drugs not already recognized to be safe *and effective*; and for such drugs they would have to convince the FDA that such drugs were in fact both safe *and effective*. As we explain below, part III (A), the explicit efficacy requirement is not just a means of providing economic protection to consumers but is an

[5] Brief for the United States in *Bentex*, at 7-8 and n. 16.

integral part of a genuine guarantee to the public that all drugs on the market are really safe. Third, Congress required that the safety and efficacy of "new drugs" be demonstrated by "substantial evidence." In furtherance of this goal, it defined with great care in the Amendments what type of evidence would be considered in evaluating efficacy: only "adequate and well controlled [scientific] investigations" could be accepted by FDA in support of manufacturers' claims. FDA was also given power to promulgate regulations to implement these new provisions.[6]

With respect to drugs that were already on the market before 1962, Congress thought it would be unfair to apply the new efficacy standard to those that had never been subject to "new drug" pre-market clearance under the 1938 Act because they were already generally recognized as "safe" when first marketed (so long as manufacturers did not suddenly begin making new claims of effectiveness for these drugs). Consequently, Congress added to the Act § 107(c)(4), exempting from the 1962 amendments drugs that (A) were sold in the United States prior to 1962, (B) were not "new drugs" under the original Act, i.e., were generally recognized as safe *and* (C) were "not covered by an effective [new drug] application." As the Senate Committee Report put it:[7]

> Drugs which are used commercially at the time of enactment and which were never subject to the "new drug" procedure before, shall not be considered "new drugs" by reason of the new "effectiveness" requirements added . . . by the bill.

In explaining this clause on the Senate floor, Senator Eastland said: "Established drugs which have never been required to go through new drug procedures will not be

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[6] § 701(a), 21 U.S.C. § 371(a).

[7] S. Rep. No. 1744, part 2, 87th Cong., 2d Sess. at 5.

affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366.

But, as to drugs that were not generally recognized as safe when first marketed between 1938 and 1962 and had therefore come within the purview of the 1938 Act's pre-marketing clearance procedures, Congress determined that the new efficacy standard *should* apply. Manufacturers of such pre-1962 drugs already cleared for safety were given a two-year grace period to perform or commission whatever studies might be necessary to produce evidence of efficacy and submit such evidence to FDA. During the interim, they could remain on the market. Then, beginning in 1964, the Amendments mandated FDA in no uncertain terms to withdraw outstanding clearance to previously approved pre-1962 "new drugs" for which there was no "substantial evidence" of efficacy as carefully defined in the statute, and to take such drugs off the market.

Although Congress clearly intended that beginning in 1964 ineffective pre-1962 drugs would be removed from the market, the fact is that the 1962 Drug Amendments remain substantially unenforced as to such drugs ten years later. *American Public Health Association* v. *Veneman, supra.* FDA did little concerning pre-1962 drugs until 1966. It then referred the preliminary task of evaluating the efficacy of these drugs to a specially established Drug Efficacy Study Group of the National Academy of Sciences—National Research Council (NAS-NRC), to whose 30 expert panels manufacturers submitted their evidence concerning their drugs' effectiveness. The NAS-NRC Study Group considered approximately 4000 pre-1962 "new drugs" with were still being marketed and on which effective NDA's were still outstanding. (The Study Group did not specifically consider any "me-too" drugs that had not been NDA'd.) On account of its rigor and the prestigious credentials of its

panel members, the Study Group's evaluation has been generally regarded as one of the most thorough and unassailable of its kind ever conducted. Of the more than 16,000 claims of effectiveness made for the 4000 drugs the Group considered, it found that less than 30% were supported by "substantial evidence" as defined in the Act. See Brief for the United States in *Bentex*, at 18-19.

Not until 1968 and 1969 did FDA begin to take action with respect to these ineffective pre-1962 drugs. Of the 70% of claims found by the NAS-NRC to be unsupported by "substantial evidence," or up to 2800 ineffective NDA'd pre-1962 drugs, FDA has issued "opportunity for hearing" notices to only about 1300, and notices of withdrawal to only about 570.[8]

Nine months ago, in an action instituted by two of the *amici curiae*, the United States District Court for the District of Columbia held that the FDA had engaged in "intolerable procrastination" in evaluating the Study Group's reports, that hearings have been subject to "interminable delay", that FDA had extended the two-year grace period provided by Congress "far beyond that envisioned by statute," and that it had "effectively stay[ed] implementation of the Congressional mandate that drugs in the market-place be both safe and effective." *American Public Health Association* v. *Veneman*, CA No. 1847-70 (August 23, 1972). The Court retained jurisdiction and established a time schedule for FDA to complete its enforcement of the 1962 Amendments as to pre-1962 drugs. (Order of Bryant, J., October 11, 1972).

Thus, eleven years after Congress acted to remove ineffective drugs from the market, and nine years after the date Congress set for accomplishment of that task thousands—if "me-too's" are included, tens of thousands—

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[8] Information received March 27, 1973, by *amici* from FDA's Office of the General Counsel.

of ineffective pre-1962 drugs are still being sold throughout the country to unsuspecting consumers.

Enforcement of the 1962 Amendments against these pre-1962 ineffective drugs is no mere "residual" problem, for pre-1962 drugs constitute the vast bulk, perhaps 75-90%, of all prescription drugs on the market today.[9]

II. THESE CASES PRESENT THREE DISTINCT BUT INTERRELATED LEGAL ISSUES THAT ARE CRUCIAL TO MEANINGFUL ENFORCEMENT OF THE 1962 AMENDMENTS.

The four cases now before the Court raise three distinct legal issues concerning enforcement of the 1962 Amendments with respect to pre-1962 "new drugs". Simply stated, these are:

> (1) Whether pre-1962 "me-too" drugs (for which manufacturers never formally submitted NDA's, but which were marketed on the strength of the NDAs granted their "pioneers") can escape the efficacy requirement of the 1962 Amendments by virtue of § 107(c)(4).[10]

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[9] According to information received by *amici* from FDA's Office of the General Counsel, since 1962 FDA has received only 3450 NDA's and has approved only 578 of them. Since there are still well over 2000 pre-1962 NDA'd drugs on the market, and five to 13 times as many copies of these pre-1962 drugs, see p. 13, *supra*, it is not unreasonable to estimate that 75-90% of all prescription drugs now on the market are pre-1962 drugs.

The Act is also applicable to the 100,000 to 500,000 over-the-counter drugs sold in the United States today, a substantial percentage of which may be ineffective. Enforcement against over-the-counter drugs is discussed in part III(D) of this brief, *infra*.

[10] A subsidiary issue is raised by some manufacturers' claims that a good many "new drugs" on which NDA's were actually outstanding in 1962, when the Amendments went into effect, should also be immune from the new efficacy requirements. See notes 11 and 14, *infra*.

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(2) Whether the FDA can perform the fundamental jurisdictional function of deciding, in the first instance, whether a drug is a "new drug" within the purview of the Act's pre-clearance provisions, or whether FDA has no power to determine its own jurisdiction.

(3) Whether FDA must afford a full-scale evidentiary hearing in every case before withdrawing approval of an NDA for an ineffective drug, even though the manufacturer has not submitted any evidence of effectiveness whatsoever that falls within the statutory and regulatory definitions of the type of evidence that can permissibly be considered in support of an efficacy claim.

The first issue, whether pre-1962 "me-too" drugs can escape the effect of the 1962 Amendments, arises principally in the *USV* case. Before 1962, USV marketed five citrus flavonoid drugs under outstanding NDA's and two similar "me-too" flavonoids for which it had never applied for NDA's. In 1968, FDA sought to withdraw approval of three of the five NDA's on the ground that citrus flavonoids are ineffective. It announced its view that, if successful, it would seek to remove the "me-too" flavonoids from the market as well. USV sought a declaratory judgment in District Court that all seven drugs were no longer "new drugs" in 1962 because all had become "generally recognized" as safe, and, under § 107(c)(14), were therefore not subject to the 1962 Amendments. The District Court agreed. But the Fourth Circuit reversed. It held (1) that the NDA'd drugs were clearly subject to the 1962 Amendments and (2) that although, ordinarily, "me-too" drugs never specifically covered by an NDA would not be subject to the new efficacy requirements, these particular "me-too's" were "personal" to the

company and were thus "covered" by the original NDAs on the same company's pioneer (NDA'd) drugs.[11]

The second issue, whether FDA has jurisdiction to determine what is a "new drug" under the Act, is posed in two distinct ways by the *Ciba* and *Bentex* cases, respectively: (a) whether FDA disapproval of a filed NDA operates as a judgment that the drug was in fact a "new drug" and that the NDA was in fact required to be filed under the Act, and (b) whether, when a manufacturer bypasses the FDA by failing to file an NDA and instead seeks a declaratory judgment in court that its drug is not a "new drug", the court can refer that question to the FDA for decision in the first instance.

Bentex marketed a "me-too" copy of a pioneer pentylenetetrazol combination drug on which three other companies held NDA's. In 1968, FDA sought to withdraw approval of the three NDA's, offering an opportunity for a hearing to any parties that would be "adversely affected" by such action. It issued an advisory inviting Bentex to participate in this hearing and stating its intention to withdraw Bentex's "me-too" from the market once the other manufacturers' NDA's were disapproved. Bentex and other "me-too" manufacturers then sought a District Court declaratory judgment that their "me-too's"

[11] The subsidiary issue, note 10, *supra*, is raised by USV's claim that not only its "me-too's" but at least two and possibly all five of its NDA'd drugs are also exempt. The rationale for this apparent evasion of the statutory language is that at some time before 1962 the NDA'd drugs, by virtue of their clearance and subsequent sale, became "generally recognized" as safe, were thus no longer "new drugs", and did not really need to be NDA'd any longer; consequently, the NDA's apparently covering them in 1962 were no longer "effective", and the 1962 Amendments do not apply. See note 14, *infra*.

Hynson, in its cross-petition, No. 72-414, makes a similar claim for its drug Lutrexin.

Bentex also involves a "me-too" drug, but only threshold jurisdictional questions are presented to this Court in that case.

were not "new drugs". The District Court held that both it and FDA had concurrent jurisdiction to decide this question and, in the exercise of its equitable powers, referred the issue to FDA for decision in the first instance. The Court of Appeals reversed and remanded, holding that the District Court had exclusive jurisdiction to decide the matter and should do so itself.

Ciba marketed its drug Ritonic under an effective NDA beginning in 1958. In 1969, the FDA sought to withdraw approval of the NDA for lack of substantial evidence of effectiveness. At this point, Ciba began a declaratory judgment suit in District Court for a declaration that Ritonic had, before 1962, ceased to be a "new drug". (Meanwhile, the FDA withdrew its approval, Ciba took a direct appeal from this withdrawal to the Second Circuit Court of Appeals, and that Court affirmed the FDA's action. *Ciba-Geigy Corporation* v. *Richardson*, 446 F.2d 466 (C.A. 2, 1971). FDA moved to dismiss the District Court action on the ground that, in the withdrawal proceedings, it had already determined the underlying issue adversely to Ciba. The District Court agreed and dismissed the action, and the Court of Appeals for the Third Circuit affirmed.[12]

The third or "hearing" issue arises in *Hynson*, No. 72-394. In May, 1970, the FDA promulgated regulations establishing minimum standards for "adequate and controlled investigations" required by the statute to be submitted in support of claims of "substantial evidence" of efficacy. 21 C.F.R. § 130.12(a)(15), as amended, 35 Fed. Reg. 7251, 7252. These regulations listed specific criteria for such evidence and provided, *inter alia*, that if a man-

[12] The second issue purportedly arises in *Hynson* as well, where the manufacturer is in the peculiar position of supporting FDA jurisdiction. But it is presented in a peripheral and beclouded fashion, and the courts below did not see fit even to address the question there.

ufacturer submitted no data meeting these criteria FDA would not hold an evidentiary hearing since there would in fact be nothing to hold a hearing about. Hynson, after losing (on primary jurisdiction grounds) a declaratory judgment action by which it sought District Court exemption for its drug Lutrexin (*Hynson*, J.A. I, 26), then sought a hearing from the FDA on "substantial evidence" of Lutrexin's effectiveness. After examining the evidence submitted by the company, however, FDA determined that each item failed to meet the criteria set out in the regulations; consequently, it denied Hynson a full evidentiary hearing. On petition for review, the Court of Appeals for the Fourth Circuit reversed. While ostensibly approving the FDA's regulations, the Appeals Court thought that Hynson's evidence presented a "genuine and substantial issue of fact" whether Lutrexin was "effective", and therefore Hynson should get a full evidentiary hearing.

III. A DECISION ADVERSE TO FDA ON ANY OF THESE ISSUES WILL, AS A PRACTICAL MATTER, PREVENT EFFECTIVE ENFORCEMENT OF THE ACT AND THWART THE CONGRESSIONAL PURPOSE TO REMOVE INEFFECTIVE DRUGS FROM THE MARKET.

Each of the three legal issues identified above is an essential part of a single unified approach adopted by FDA to carry out the intent of Congress manifested in the 1962 Amendments. Determination of any one of these issues adversely to FDA will, as a practical matter, operate to defeat the whole approach and prevent effective enforcement of the Act. As a result, most ineffective drugs now being sold to consumers will remain on the market indefinitely. Moreover, enforcement of the Act with respect to "new drugs" coming on the market for the first time now and in the future would also be threatened.

A. The Efficacy Requirement Added By The 1962 Amendments Is An Important Protection For Consumers.

The 1962 Congressional mandate that all drugs be not only "safe" but "effective" was not designed only to protect consumers' economic interests, though that is obviously one of its benefits. Congress and FDA recognized early on in their experience with the 1938 Act that a drug's effectiveness is often related to its safety, in the broadest medical and consumer sense.

A drug's effectiveness is an important consideration to be taken into account when it is known to have serious side effects. More generally, however, we are increasingly coming to realize that *all* drugs involve some risk of danger to some persons under some circumstances. The risk to all consumers is increased many-fold—and is not acceptable—when they are encouraged to consume a vast quantity of drugs that are really ineffective. Moreover, in many cases reliance on an ineffective drug excludes or makes less likely administration of an alternative drug (or therapy) that is badly needed and *would* be effective, thus posing a direct threat to health or, in the case of life-threatening diseases, to life itself.

B. A Decision Adverse To FDA Will Frustrate Enforcement Of The 1962 Amendments As To Pre-1962 Drugs.

(1) *If "Me-Too's" Are Exempt From The 1962 Amendments.*—As noted above,[13] the vast majority of prescription drugs now on the market were introduced prior to 1962 and most of these are "me-too" drugs not specifically being marketed under approved NDA's. If the 1962 Amendments are held applicable only to NDA'd pioneers, but not to the vastly larger number of copies

[13] See p. 17 and note 9, *supra*.

produced by other companies or under different names, as the Fourth Circuit has held, FDA will be unable to protect consumers from the thousands of ineffective pre-1962 drugs currently on the market, contrary to what Congress plainly intended. Moreover, manufacturers of ineffective NDA'd pioneer drugs will simply stop marketing them, rather than face up to the new statutory requirements, and will shift their production, advertising, and marketing to non NDA'd "me-too's" which need never be shown effective under such a ruling. The few manufacturers who had not marketed copies of their own pioneer drugs will, of course, lose out. But their competitors who do market the pioneer's copies (very often the identical drug under license from the manufacturer of the pioneer) will undoubtedly take up the slack. The public, therefore, will lose out in every instance—for the great majority of versions of every single ineffective "new drug" now being sold to consumers will remain on the market indefinitely.[14] No reasonable argument has been advanced, on health or other public policy grounds, why only a few of these ineffective drugs but not the majority of drugs that are identical or substantially similar to them should be removed from the market; or why Congress would intend such a result.

(2) *If the FDA Cannot Determine Its Own Jurisdiction.*—Even if the Court agrees with FDA that pre-1962 "me-too's" should be treated on an equal footing with their NDA'd pioneers, but holds that only courts—not FDA—can decide what drugs are covered by the

[14] *A fortiori*, if this Court accepts the claims of USV and Ciba that even their NDA'd drugs should be exempted, the 1962 Amendments will be rendered a practical nullity with respect to pre-1962 drugs. Almost every pre-1962 NDA'd drug that had been marketed for any substantial period of time arguably falls within that rubric. The "exception" provided by § 107(c)(4) would then swallow the whole by exempting almost all pre-1962 NDA'd drugs as well as all of their copies.

Amendments, FDA's enforcement effort against pre-1962 drugs could be long delayed or even rendered futile. And the courts will be flooded with litigation turning on highly technical medical, chemical, and pharmacological evidence.

Petitioner in *Ciba* argues that FDA disapproval (for lack of efficacy) of an NDA filed and approved by FDA prior to 1962 does not establish that the drug was really a "new drug" for which an NDA had to be filed in the first place, and that only a District Court is entitled to determine that jurisdictional point. If this Court holds that pre-1962 "me-too's" should be treated like their pioneers, but agrees with Ciba, then every manufacturer of a pre-1962 NDA'd drug whose clearance is now withdrawn by FDA (and who fails to win reversal of FDA action on petition for review to the Court of Appeals) will be entitled to litigate *de novo* in the District Court the question whether its drug was a "new drug" subject to the 1938 Act in the first place. Since this result would accord manufacturers a 'free second chance', several thousand District Court actions are likely. In each, the District Court will be obliged to consider a mass of pre-1962 medical and pharmacological data, and to determine whether at some point prior to 1962 the NDA'd drug became "generally recognized" by "qualified experts" as "safe". A judgment for the manufacturer in such a case would render the prior lengthy administrative proceeding concerning the drug's efficacy, and Court of Appeals review of that decision, a mere irrelevancy.

This Court could (and should) foreclose this possibility by holding, in accord with clear Congressional intent, not only that pioneers and copies should be treated alike but also that *all* pre-1962 drugs on which NDA's were outstanding in 1962 (and all their copies) automatically are subject to the efficacy requirements.

Such a holding might not, however, entirely counteract the effect of the Fourth Circuit's jurisdictional ruling in

Bentex. There, manufacturers of "me-too's" that had never been NDA'd sought a court judgment that their drugs were not "new drugs" and were not covered by the Amendments. The Fourth Circuit held that the threshold jurisdictional question could not be referred to the FDA but must be decided by the District Court. Presumably a decision by this Court that all copies of NDA'd pioneers are definitely covered by the Amendments would deprive "me-too" manufacturers of the core of their legal argument. But who is to decide when a drug is really a "me-too", i.e., when it is so "substantially similar" to a pioneer that FDA's withdrawal of the pioneer operates as a judgment about the alleged copy as well? The import of *Bentex* is that only the courts—not FDA—have the power to decide when a drug is really a "me-too" and therefore, like its pioneer, should be treated as a "new drug".

Should the Court leave this loophole open, it is likely that most manufacturers of pre-1962 "me-too's" whose NDA'd pioneers are removed from the market will come to the District Courts seeking to show that their products are not really copies but are in some way different from the pioneers, thus ought not to be characterized (like the pioneers) as "new drugs", and should not be subjected to the efficacy requirements. This could involve the District Courts in a deluge of tens of thousands of actions. Under the ruling in *Bentex*, the District Courts would apparently have no option to transfer the technical issue involved to FDA. They would have to decide it themselves, on the basis of medical, chemical, and pharmacological data of the type FDA regularly considers in making judgments about these drugs, but with which courts are simply not equipped to deal.

The only sensible approach to these problems is for District Courts to refer to FDA, for decision in the first instance, the questions of whether a drug is a "new

drug", and whether a purported copy is indeed "substantially similar" to its pioneer. These are precisely the types of judgments administrative agencies are supposed to make and can make, especially where scientific information of such a highly technical nature is involved, as here.

Retention of this jurisdictional power in FDA will preserve judicial review of the agency's judgments, both on petition for review to the Court of Appeals from disapproval of an NDA (available to both the pioneer and to all manufacturers of copies, who are invited under FDA regulations to participate fully as parties, *see* 37 Fed. Reg. 23185, adding § 130.40 to 21 C.F.R.) and in actions for seizure or injunction by FDA when a "me-too" manufacturer refuses to withdraw his product. But the standard of review will be no different from that which courts are accustomed to employ in overseeing expert administrative agency action.

(3) *If Hearings Must Be Accorded In Every Case, However Pointless*—Finally, if this Court agrees that FDA has statutory authority and jurisdiction to enforce the 1962 Amendments against both pioneer and "me-too" drugs, but rules that FDA must afford a full-scale evidentiary hearing to every manufacturer who submits a mass of 'scientific' evidence in support of its product's efficacy even though none of that evidence meets the threshold criteria of the statute and regulations, FDA may never be able to fulfill its statutory responsibility.

Of the 4000 NDA'd drugs reviewed by the NAS-NRC Study, the effectiveness of only 434 was found to be supported by "substantial evidence". Thus up to 3500 ineffective NDA'd drugs are subject to withdrawal under the 1962 Amendments. If the decision of the Fourth Circuit in *Hynson* is upheld, the prospect that most manufacturers of these ineffective drugs will seek and be able to obtain full-scale evidentiary hearings and that thou-

sands of these hearings will have to be held, is not unrealistic. The clear import of the Fourth Circuit's view is that *any* manufacturer who produces a large quantity of evidence of any kind that, to the layman's eyes, seems to support the efficacy of its product will be entitled to a full-dress hearing. And almost every manufacturer that desires to keep marketing an ineffective pre-1962 drug will, in fact, be able to produce enough testimonial, anecdotal, and other unscientific evidence to meet the standard articulated by the Fourth Circuit.

The legislative history and the language of the Act itself, which the Fourth Circuit appears to have disregarded, establish that this is manifestly not what Congress intended. Congress was well aware that masses of documentary evidence, uncontrolled scientific studies, and reports of experiments lacking systematic selection procedures and statistical analysis could be marshalled by most manufacturers, and sought statutorily to exclude such evidence from any consideration. Yet the Fourth Circuit's decision in *Hynson* reads out of the statute Congress's own definition of "substantial evidence" and replaces it with a judicially-fashioned, layman's definition that Congress deliberately rejected.

FDA simply does not have the resources or staff to hold in the next few years the thousands of pointless hearings that would be required if the Fourth Circuit's view is sustained. Some NDA's now run to 400 volumes of scientific data, and the average in 1970 was about 30 volumes, or a stack of paper 10-12 feet high. See Brief for the United States in *Bentex*, at 9, n. 18. The average time for a hearing may be as long as a month. FDA has noted that one recent hearing took three months to complete. *In the Matter of SERC Tablets, Unimed Inc.*, Docket No. FDCD-111, 1969.

Nor will FDA be able to comply with the implementation schedule imposed on it by the District Court in

American Public Health Association v. *Veneman, supra.* In its petition for a writ of certiorari in *Hynson*, the FDA stated that "[m]anifestly, the agency will be unable to satisfy the thrust of [the *Veneman* decision] to expedite review and appropriate withdrawal actions if it must meet the standard for granting evidentiary hearings prior to withdrawal that has been imposed [by the decision below]." In its brief as Petitioner in *Hynson*, the United States further observes that FDA is "currently laboring to carry out the court's order [in *Veneman*] punctually, but its efforts will be of little avail and of no benefit to the public if all that is accomplished is to bring nearer the holding of hundreds or thousands of pointless hearings." Page 30.

If this Court requires FDA to evaluate in full-scale evidentiary hearings evidence that Congress itself statutorily excluded in 1962 as inadequate, the Congressional intent will be subverted and the delay in enforcing the 1962 Amendments will be interminable.

C. An Adverse Decision Will Also Threaten Enforcement of the 1962 Amendments With Respect to Post-1962 Drugs.

The Fourth Circuit decisions also threaten to block effective enforcement of the 1962 Amendments with respect to "new drugs" now coming on the market.

FDA now regards all "me-too" copies of post-1962 "new drug" pioneers to be themselves "new drugs" requiring premarketing clearance.[15] Manufacturers of new "me-too's" must now file 'abbreviated' NDA's (which can refer to the pioneer) on each such drug. If, as USV and Ciba argue, *see* notes 10, 11, and 14, *supra*, marketing of a new drug pioneer for a short period of time under an effective NDA makes that drug *ipso facto* no longer

[15] 37 Fed. Reg. 23185, adding § 130.40 to 21 C.F.R.

a "new drug", and if copies introduced more than a few months or a year after the pioneer need not be NDA'd, then the reach of FDA's enforcement will extend to only a tiny fraction of the entire universe of "new drugs" coming on the market. And such a holding would simply encourage manufacturers to abandon pioneers after a short time and concentrate on marketing copies, which would not have to be subjected to pre-marketing clearance.

This result would undermine FDA's important "continuing enforcement" function. Section 505(e)(3) of the Act, as amended in 1962, now requires the Secretary to withdraw approval of an NDA if he finds on the basis of "new information" that the drug is not safe or effective. Continuing jurisdiction over NDA'd drugs is necessary to permit FDA to withdraw drugs hitherto thought to be safe and effective when new data comes to light casting doubt on this judgment (as it has in recent cases of food additives shown to be carcinogenic).

If FDA has no power to determine its own jurisdiction, the manufacturer of a "new drug" now being put on the market for the first time will be able to bypass or duplicate FDA clearance procedures and throw the resolution of the jurisdictional issue into the courts. For example, if the Court accepts the argument of petitioner in *Ciba*, drug manufacturers interested primarily in delay will routinely submit an NDA to FDA. Then, if FDA determines that substantial evidence of the drug's efficacy is lacking (and the Court of Appeals affirms), the manufacturer will simply repair to the District Court for a *de novo* determination of whether it had to file the NDA in the first place. The evidence considered by the District Court in deciding whether the drug was "generally recognized as safe and effective" will be virtually identical to that previously considered by FDA in determin-

ing the "substantial evidence" question.[16] If the Fourth Circuit's decision in *Bentex* is affirmed, manufacturers would have no obligation to go to FDA first but could seek a declaratory judgment in District Court that they were not required to file NDA's on particular products. The District Courts could not refer these disputes to FDA, under *Bentex*, but would have to do the FDA's job for it by deciding, on the basis of all the medical and scientific information, whether the drug was indeed a "new drug". Again, the evidence considered by the District Court would be roughly the same as the evidence the manufacturer would have submitted to FDA to show safety and efficacy had the manufacturer filed an NDA rather than gone to court.

Clearly Congress could not have intended such wasteful and confusing duplication or the ousting of FDA in favor of judicial determination of such complex technical and scientific questions.

D. The Fourth Circuit's Decisions, If Sustained, Will Undermine FDA's Aggressive New Effort to Enforce the Act, For the First Time, Against Over-The-Counter Drugs.

The 1938 Act and 1962 Amendments are fully applicable to over-the-counter (OTC) drugs, but as a practical matter FDA has never enforced the Act against these products. A substantial percentage of the 100,000 to 500,000 OTC drugs now on the market are probably ineffective, but FDA simply does not have the resources to deal with these drugs individually, as the Brief for the United States in *Bentex* points out (pp. 24-25).

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[16] *De novo* District Court consideration of whether the drug was a "new drug" would give the manufacturer a second chance at review of this precise question, since the jurisdictional issue can be raised in the Court of Appeals on petition to review FDA's disapproval of a filed NDA. See Brief for United States in *Bentex*, at 53-55.

In the past year, FDA has taken encouraging new steps to deal with ineffective OTC drugs. Pursuant to new regulations, 37 Fed. Reg. 85-86, 9464, 9475, FDA proposes to classify the various drugs by therapeutic class and to investigate the claims of each class to effectiveness. This is a sensible approach to OTC drugs because the dimensions of the "me-too" problem with respect to such drugs are so great. Hundreds or thousands of drugs marketed under different names by different companies in fact contain identical active ingredients, and many more are familiar combinations of active ingredients contained in many other products. FDA's investigations of OTC drugs will accomplish two important goals. First, they will identify potential subjects for misbranding actions and provide the scientific evidence of ineffectiveness FDA needs for such actions but seldom possesses.[17] Second, they will permit FDA in the future to classify as "new drugs" all OTC drug substances shown by the investigations to be ineffective and to prevent new versions or copies of these drugs from being marketed without express approval. The investigations, together with the new drug inventory required by the Drug Listing Act of 1972, 86 Stat. 559 (see Brief for the United States in *Bentex*, at 23-24), will also permit FDA to identify and withdraw from the market ineffective OTC drugs brought on the market after 1962 for which manufacturers never applied for NDA's.

The Fourth Circuit's approach to the Act would, however, blunt this significant new enforcement effort before it gets off the ground. If, as the Fourth Circuit believes, the Act permits FDA to deal only with an original pioneer and not with copies, and if FDA has no jurisdiction to decide what is a "new drug" or when a drug is a copy, then FDA's endeavor to classify and withdraw ineffec-

[17] See part III(e) of this Brief, *infra*.

tive OTC drugs will be jeopardized, if not doomed to failure.

As FDA recognizes, the "class" approach, which is perfectly consistent with the Act, is the only practical way to apply the Act to the vast number of outstanding and future OTC drugs.

E. Misbranding Actions Are No Substitute For The Efficacy Requirements Adopted In The 1962 Amendments.

Petitioner USV suggests (p. 64) that the FDA's statutory authority to deal with "misbranded" drugs, especially through an action for condemnation in District Court,[18] will be quite adequate to protect the public interest in drug efficacy if the 1962 Amendments are gutted by judicial action. Obviously, if Congress believed this to be the case it would never have enacted the 1962 Amendments, and if FDA thought "misbranding" actions were effective tools it would not be attempting to enforce the 1962 Amendments.

In fact, for two reasons, the misbranding action is so difficult and drawn out that it is practically useless. First, the burden of proof in such an action is on the Government, and the task of proving positively that a drug is *in*effective (even by a preponderance of the evidence) is a considerable one. Second, in a court action there are no limitations on the type of evidence the manufacturer can submit, however unscientific it may be. A mass of testimonial and anecdotal evidence from doctors of the type Congress believed should not be considered by FDA to show efficacy can be introduced in court in defense of a misbranding action. This evidence may appear to judge and jury to be a powerful rebuttal to the Government's case.

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[18] 21 U.S.C. §§ 331(a), 334(a).

Consequently, to prevail in a misbranding action, the FDA has found it necessary to conduct its *own* careful scientific study of the drug in question to establish ineffectiveness. Such studies are costly and often take several years. And even a very good study may fail to impress the judge or jury in light of the mass of contrary (unscientific) evidence submitted by the manufacturer.

IV. FDA'S ENFORCEMENT PROGRAM IS TOTALLY CONSISTENT WITH THE STATUTORY LANGUAGE AND HISTORY.

A. Congress Intended The 1962 Efficacy Requirement To Apply To Both Previously NDA'd Drugs And Their Copies.

The legislative history of § 107(c)(4), discussed at pp. 14-15, *supra*, and in the Brief for the United States in *Bentex*, at 10-14, shows that Congress meant to exempt from the efficacy requirement only "old drugs"—those generally recognized as safe when first marketed—that had never come within the ambit of the "new drug" provisions of the 1938 Act. There is no extrinsic evidence to show that Congress was aware of the "me-too" problem or of the possibility that its exemption clause might be held applicable not just to old drugs but to copies of "new drugs". The best interpretation of what Congress intended is that which is most sensible and harmonious with the statutory purposes. Here, the interpretation most harmonious with the purposes of the Act is that Congress did not intend by § 107(c)(4) to provide a loophole for copies of "new drugs", but that it simply meant to exempt old drug substances that were never affected by the original clearance scheme. The contrary interpretation would not only defeat the purpose of the 1962 Amendments; it makes little practical sense. It would create the incongruity of having two different statutory clearance standards for the identical drug substance, depending on the name under which the substance was marketed. Which

standard was applicable would depend not on any rational or public policy ground, but on the regulatory history of the drug as determined by the manufacturer. The resulting irrational discrimination rebuts the notion that this is what Congress intended.

The language of § 107(c)(4) exempts only pre-1962 drugs that were not "covered by" an effective NDA. USV's lengthy argument that the NDA's covering pioneers were "personal" to those drugs, however valid, misses the point. The issue is what Congress *intended* by the words "covered by" as used in the section, words that appear nowhere else in the Act. Though most "me-too's" were marketed without the formal filing of applications for clearance, they were obviously marketed on the strength of the clearances previously granted their identical (or substantially similar) pioneers. As pointed out above, the only sensible interpretation of Congressional intent consistent with the purposes of the Act is that "me-too's" were "covered by" the NDA's of their pioneers, and that copies are no more exempt from the efficacy requirement than their pioneers just because they are marketed under different trade names.

The manufacturers argue that until recently FDA has appeared to adopt their view concerning the reasons NDA's were not required to be filed on most "me-too's" and that the agency has now changed its mind. Though FDA has altered its explicit requirements for filing of NDA's on "me-too" drugs, it appears to *amici* that in practical terms the agency has been perfectly consistent in its overall enforcement approach. Before 1962, when clearance of a filed NDA occurred automatically absent FDA objection, the FDA informally cleared "me-too" copies once the pioneer was cleared. By the terms of the 1938 Act, FDA should at least have required manufacturers of the copies to file abbreviated NDA's as it does now. But its failure to do so was primarily an accom-

modation to the manufacturers and had no adverse consequences to the consumer. The consumer was protected by the fact that the pioneer was required to be NDA'd. The pioneer and the "me-too's" rose and fell together.

In 1962, FDA was required by its new statutory mandate affirmatively to investigate the efficacy of all pre-1962 "new drugs." FDA again wishes to insure that pioneers and "me-too's" rise and fall together in order to protect the consumer. But it can no longer protect the consumer if it ignores the statutory scheme and does not formally designate "me-too's" as "new drugs". Therefore, FDA now correctly insists that "me-too's" are "new drugs" within the meaning of the 1938 Act and 1962 Amendments.

In short, FDA previously engaged in an administrative practice inconsistent with the terms of the 1938 Act as an accommodation to manufacturers and at no cost to consumers. The consumer, whom the Act seeks to protect, should not now be penalized for FDA's erroneous view of what the statute required it to do with respect to "me-too's". And FDA itself should not be prevented from now adopting a correct interpretation of the Act in order to fulfill its purpose of protecting consumers.

The change from prior improper practice does not prejudice those who contest the change or defeat any *reliance interest* they may have developed. The drug manufacturers have not acted or been encouraged to act in reliance upon FDA's previous administrative interpretation. If anything, they benefited from it undeservedly. The only interest they now assert is the interest in continuing to market ineffective drugs ten years after Congress directed that such drugs be taken off the market. It would not defeat any valid interest of the drug manufacturers for this Court to uphold FDA's present strict adherence to the statutory scheme and to prevent sub-

stantial detriment to the public resulting from FDA's erroneous past administrative practice.

USV's most vehement arguments are directed against actions FDA has not yet taken. (1) USV claims the FDA has no specific statutory authority to "withdraw" or force off the market a drug that has never been NDA'd. To the contrary, FDA does have power under the statute to go to court to do just that. And traditionally it has advised manufacturers whether their drugs are "new drugs", and thus need to be NDA'd. The obvious consequences of such an advisory opinion, if ignored, are that FDA may seek District Court action against the manufacturer. Thus FDA anticipates doing in the future only what it has been doing all along in order to make the system work for both the public and manufacturers. (2) USV also attacks the hearing procedures FDA intends to put into practice for adjudicating the efficacy of both a pioneer and its copies in a single proceeding. But these regulations are not before this Court, and their legal sufficiency can be challenged elsewhere.

B. FDA Has Jurisdiction To Decide, In The First Instance, What Is A "New Drug" And When A Drug Is A Copy.

Two jurisdictional issues are posed by these cases: whether FDA action on a filed NDA operates as a judgment that the drug was in fact a "new drug" for which an application had to be filed; and whether, when a drug manufacturer seeks a declaratory judgment in District Court that its product is not a "new drug", the Court may refer that question to FDA for decision in the first instance.

With respect to the first issue, the only sensible answer is that FDA does determine its own jurisdiction in the context of its own administrative proceeding. This conclusion is supported by precedent. This Court has, in-

deed, recently held that where an agency's threshold jurisdiction turns on technical questions of fact arguably within the competence of the agency, it "should at least be requested to institute proceedings" [in the course of which the agency would determine the question of its jurisdiction]. *Ricci* v. *Chicago Mercantile Exchange*, No. 71-858 (Jan. 9, 1973); *see Marine Engineers Beneficial Assn.* v. *Interlake S.S. Co.*, 370 U.S. 173; *Federal Power Commission* v. *Louisiana Power & Light Co.*, 406 U.S. 621 (1972). The conclusion is supported by logic, since the function of the administrative agency to resolve technical, factual issues requiring special expertise is equally applicable to determining, within a fairly broad scope, the facts upon which its jurisdiction depends. And the conclusion is supported by the nature of the decisions called for by the clearance scheme involved here. Under the 1962 Amendments, the "new drug" threshold jurisdictional issue (i.e., whether a drug is "generally recognized" as effective) and the "substantial evidence of effectiveness" issue are similar questions whose resolution turns upon practically the same evidence. Moreover, both turn on highly technical medical, chemical and pharmacological judgments. It would be unreasonable to assume that the Act obligates FDA to make one of these judgments but bars FDA from making the other judgment, permitting only a court to do that. We have argued in part III, *supra*, that this would be wasteful, confusing, and deleterious to enforcement of the Act. It would also be contrary to the well-established role of administrative agencies.

With respect to the second issue, District Court deferral to FDA is supported by all the considerations mentioned above. See also *Ricci* v. *Chicago Mercantile Exchange*, *supra*; *United States* v. *Western Pacific R. Co.*, 352 U.S. 59; *Far East Conference* v. *United States*, 342 U.S. 570. Moreover, referral is consistent with the overall

scheme of the Act. It encourages the manufacturer to go first to FDA with a new drug application, since the manufacturer knows that the agency will be deciding the issue in the first instance anyway. A contrary holding would tend to undermine the self-policing nature of the Act by permitting manufacturers to choose the forum they preferred for resolution of the "new drug" issue.

C. FDA Need Not Accord A Full Evidentiary Hearing When The Manufacturer Produces No Scientific Studies That Meet The Statutory And Regulatory Criteria.

Congress defined "substantial evidence" in the 1962 Amendments with a high degree of particularity, as the statutory language and legislative history (set out in the Government's Brief in *Hynson*, No. 72-394, at 15-17) demonstrate. Only "adequate and well-controlled investigations" could be accepted in support of efficacy claims. The Committee Report on the bill provides further details of what Congress meant by this definition:

> A claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations. S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 6.

Congress was well aware that masses of documentary evidence, uncontrolled scientific studies, and reports of experiments lacking systematic selection procedures and statistical analysis could be marshalled by most manufacturers, and sought statutorily to exclude such evidence from any consideration. The Act authorizes FDA to promulgate regulations to implement the efficacy requirements, 21 U.S.C. § 371(a), and FDA's regulations set-

ting out criteria for "substantial evidence" are firmly rooted in the Act, the legislative history, and the best current scientific thinking. *See*, 21 C.F.R. 130.12(a)(15) and 130.14, as amended, 35 Fed. Reg. 7251, 7252. These regulations have uniformly been upheld by the courts [19] and are ostensibly not challenged here by any party.

However, the decision of the Fourth Circuit in *Hynson*, if allowed to stand, will nullify the regulations by reading out of the 1962 Amendments Congress's own definition of "substantial evidence" and replacing it with a generalized layman's definition that Congress deliberately rejected. The Fourth Circuit ruled that Hynson was entitled to a full evidentiary hearing because its evidence raised a "genuine issue of fact" concerning its drug's efficacy, even though FDA found none of this evidence to be of the type that was entitled to any consideration under the statute and regulations. By so holding the court addressed itself to the wrong question. The statute does not envisage that *any* number of inadequate, uncontrolled studies could be sufficient to show efficacy. The proper issue on review had nothing to do with what the studies showed (i.e., whether the studies presented some evidence of efficacy). The proper issue was whether they were the kinds of studies the statute and regulations permit FDA to consider in support of an efficacy claim. This is a *legal* question FDA must decide in the first instance. FDA's legal judgment is fully reviewable on appeal. But its determination that none of the studies presented by Hynson met the criteria for consideration compelled the conclusion that there was nothing before it upon which a determination of "substantial evidence" —as defined in the statute—could be premised. In similar contexts, the courts have upheld agency denial of a

[19] *Upjohn* v. *Finch*, 422 F.2d 944 (CA 6, 1970); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970); *see also* cases cited in note 1, *supra*, and the decisions below in the instant cases.

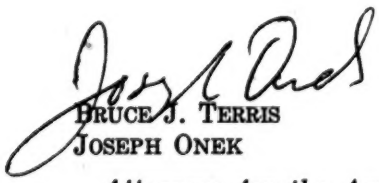
hearing. *See, e.g., Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33, and other cases cited in the Brief for the United States in *Hynson*, No. 72-394, at 22-23.

Consequently, FDA was perfectly correct in denying Hynson an evidentiary hearing in this case.

CONCLUSION

For the foregoing reasons, the judgments of the Courts of Appeals in *Hynson*, No. 72-394, and *Bentex*, No. 72-555 should be reversed, and the judgments in *USV*, No. 72-666, *Hynson*, No. 72-414, and *Ciba*, No. 72-528 should be affirmed.

Respectfully submitted,



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